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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,645	08/01/2003	Linda B. Couto	51271/35:1	5318

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/632,645	COUTO ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 6-11* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4, and 6-11 are pending.

The amendment to claims 1 and 9-10, the sequence listing, and the amendment to the specification filed on 1/22/07 is acknowledged and considered by the examiner.

Election/Restrictions

Claim 4 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/9/06.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder et al. (US 2002/0155580, cited on an IDS) taken with Simonet (US Patent No. 6,268,212, cited on an IDS). Snyder teaches a virus particle comprising a recombinant AAV vector comprising a promoter operably linked to a polynucleotide encoding a polypeptide comprising the factor VIII 90kD heavy and light chain with the B-domain deleted (pages 5-12). Snyder teaches that the promoter can be tissue specific for the liver (page 4). Snyder further teaches that one of ordinary skill in the art will appreciate that a tissue-specific promoter for use in the AAV vector may be selected from any of the known liver-specific promoters (page 4). However, Snyder does not specifically teach a composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a B-domain deleted human Factor VIII protein operably linked to a liver specific promoter, wherein the liver-specific promoter is the transthyretin (TTR) gene promoter.

However, at the time the invention was made, tissue specific promoter, specifically liver-specific promoters (e.g. TTR) were well known in the art for use in enhancing liver expression of a transgene using a vector as exemplified by Simonet. Simonet teaches several liver-specific

promoters (e.g. TTR) that could be used in producing a vector comprising a transgene operably linked to a liver-specific promoter (column 3, line 64-column 4, line 12 and abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made to combine the teaching of Snyder and Simonet to make a composition comprising a recombinant AAV comprising a nucleotide sequence encoding a B-domain deleted human Factor VIII protein operably linked to a liver specific promoter TTR. One of ordinary skill in the art would have motivated to make the claimed composition because factor VIII is expressed in the liver and the promoter TTR used to increase gene expression of a vector in the liver.

In view of the teaching of Snyder and Simonet for producing a vector comprising a tissue specific promoter operably linked to a nucleic acid, one of ordinary skill in the art would have had a reasonable expectation of success for producing the claimed rAAV vector.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 1/22/07 have been fully considered but they are not persuasive.

In response to applicant's argument that the office has not provided a specific motivation for combining Snyder and Simonet, the argument is not found persuasive because one of ordinary skill in the art would have motivated to make the claimed composition because factor VIII is expressed in the liver and the promoter TTR used to increase gene expression of a vector in the liver. See In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., high level of transgene expression) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, even if the claims recited the limitation, the applicant has not provided any evidence of record to support applicant's assertion. See In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Furthermore, if the claims recite the limitation, the claims would be directed to a product taught in the prior art having the same structure. See STX LLC. v. Brine, 211 F.3d 588, 591, 54 USPQ2d 1347, 1350 (Fed. Cir. 2000). Also see In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). This is the case here, the rAAV vector comprising the heavy and light chain of factor and the TTR promoter were known in the prior art.

In response to applicant's argument that the office has not provided a reasonable expectation of success for producing the claimed invention, the argument is not found persuasive because Snyder teaches producing a rAAV vector comprising a promoter operably linked to a

polynucleotide encoding the heavy and light chain of Factor VIII. Constructing a rAAV vector comprising a promoter was taught by Snyder and the TTR gene promoter was taught by Simonet. One of ordinary skill in the art would have a reasonable expectation of successfully cloning the TTR promoter into the vector taught by Snyder. See Ex parte Blanc, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989).

Claims 1 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder and Simonet as applied to claims 1 and 11 above, and further in view of Almstedt et al. (WO 91/09122, cited on an IDS).

However, Snyder and Simonet do not specifically teach a composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a functional Factor VIII, wherein the nucleotide sequence encodes a heavy and a light chain of Factor VIII with the B domain deleted, and wherein said light chain and heavy chain of Factor VIII are operably linked to a junction having SEQ ID NO: 15.

However, at the time the invention was made, a recombinant factor VIIII protein comprising a first DNA segment coding for the 90kDa chain and a second DNA segment coding for the 80kDa chain of human factor VIII, wherein the segments were interconnected by a linker DNA segment coding for a linker peptide of 4 to about 100 amino acid residues (having SEQ ID NO: 15 of the instant claims) was well known in the art as exemplified by Almstedt (abstract). Almstedt further teaches that the DNA sequence can be expressed in recombinant expression vectors (abstract). In addition, Almstedt teaches that the smallest active form (one heavy chain and one light chain) with a molecular weight of 170kDa could be activated by thrombin to the

same extent as the high molecular weight forms and there was an indication that that smaller form has a 50% longer survival time compared to the higher molecular form (page 4).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention made to combine the teaching of Snyder and Simonet in further view of Almstedt to make a composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding a B-domain deleted Factor VIII protein, and wherein said nucleotide sequence further encodes a junction (SEQ ID NO: 15) that operably links said heavy and light chain of Factor VIII. One of ordinary skill in the art would have motivated to make the composition because Almstedt teaches that the smaller form of Factor VIII comprising both chains has a 50% longer *in vivo* survival time compared to the higher molecular forms of Factor VIII.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments, see page 4, filed 1/22/07, with respect to the rejection(s) of claim(s) 1 and 6-8 under 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendment to claim 1.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 6-11 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,200,560. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim from the instant application and the claims from '560 are both directed a recombinant adeno-associated virus comprising a nucleotide sequence encoding a Factor VIII protein operably linked to a promoter.

The claims from '560 do not specifically recite a nucleotide sequence encoding a Factor VIII lacking at least a portion of the B domain. However, in view of the definition of Factor VIII in the specification of '560, the claims of '560 read on the instant claim because the specification teaches that Factor VIII is lacking a B domain (Figure 3). See MPEP 804 which recites that those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent (In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)).

Applicant's arguments filed 1/22/07 have been fully considered but they are not persuasive.

Applicant request that the filing of a terminal disclaimer be postponed until allowable subject matter has been identified.

Claims 1 and 6-11 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,221,349. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim from the instant application and the claims from '349 are both directed to a recombinant adeno-associated virus comprising a nucleotide sequence encoding a Factor VIII protein operably linked to a promoter.

The claims from '349 do not specifically recite a nucleotide sequence encoding a Factor VIII lacking at least a portion of the B domain. However, in view of the definition of Factor VIII in the specification of '349, the claims of '349 read on the instant claim because the specification teaches that Factor VIII is lacking a B domain (Figure 3). See MPEP 804 which recites that those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent (In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)).

Applicant's arguments filed 1/22/07 have been fully considered but they are not persuasive.

Applicant request that the filing of a terminal disclaimer be postponed until allowable subject matter has been identified.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 6:30 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Douglas Schultz, PhD, SPE – Art Unit 1635, can be reached at (571) 272-0763.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of

such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Brian Whiteman